Amendments to the Specification:

On page 1, before line 1, insert as a new paragraph and subsequent heading:

This application is a 371 national phase of PCT/GB2003/005171, filed November 28, 2003, and published in English as WO 2004/050708 on June 17, 2004.

Background of the Invention

Page 4, after line 17, insert the following:

Summary of the Invention

The present provides a binding partner for TSH receptor. The binding partner comprises or is derived from

(a) a human monoclonal antibody reactive with the TSH receptor;
(b) a recombinant antibody reactive with the TSH receptor; or
(c) a fragment of a human monoclonal antibody or a recombinant antibody reactive with the TSH receptor.

The binding partner of the invention can be used in therapeutic and diagnostic applications, and for identification of epitope regions on TSH receptor.

Brief Description of the Drawings

Fig. 1 shows inhibition of TSH binding to TSH Receptor in the presence of a binding partner of the invention. The control IgG was a human monoclonal antobody to GAD_{65}.

Fig. 2 shows thyroid stimulating activity of hMAb TSHR1 IgG and Baf, porcine TSH (70 units/mg; pTSH) recombinant human TSH (6.7 units/mg; hTSH) and a control monoclonal antibody (MAb; human monoclonal autoantibody to thyroid peroxidase (2G4)). Basal = cAMP prpoduced in the presence of NaCl free Hanks Buffered Salt Solution only.

Fig. 3A shows the effect of lymphocyte donor serum on inhibition of TSH binding and on cAMP stimulation in THS receptor transfected CHO cells. In the case of the binding i nhibition assay the serum was diluted in a pool of healthy donor sera. For the stimulation assay, the serum was diluted in NaCl free Hanks Buffered Salt Solution. Healthy blood donor sera (n=3) gave responses ranging from 1.1 to 1.3 X basal.

Fig. 3B shows a comparison of an ELISA for TSHR autoantibodies according to thepresent invention with earlier assays: an ELISA on TSH-biotin described in Bolton et al., Clinical Chemistry

(1999) 45: 2285-2287 and the original RIA described by Southgate et al. in Clinical Endocrinology (1984) 20: 539-543.

Fig. 3C shows a comparison of an ELISA for TSHR autoantibodies according to the present invention and an ELISA based on TSH biotin as described in Bolton et al., Clinical Chemistry (1999) 45: 2285-2287. Sera from 72 patients with Graves disease were compared. y=1.1154x - 13.032 , r=0.99.

Fig. 4 shows the nucleotide sequence of hMAb TSHR1 Heavy chain V, D and J region with the primer, CDR and constant region sites labeled (Seq ID No: 14).

Fig. 5 shows the amino acid sequence of hMAb TSHR1 Heavy chain V, D and J region with the CDR and constant regions labeled (Seq ID No: 5).

Fig. 6 shows the nucleotide sequence of hMAb TSHR1 Light chain with the primer and CDR sites labeled (Seq ID No: 14).

Fig. 7 shows the amino acid sequence of hMAb TSHR1 Light chain with the CDR sites labeled (Seq ID No: 6).

Fig. 8 shows effects of 2 patients sera (T1 and T2 with TSH antagonist activity) on stimulation of cyclic AMP production by pTSH (0.5 ng/ml) and hMAb TSHR1 IgG (10 ng/ml) and Fab (5 ng/ml) in CHO cells transfected with the TSHR.

Fig. 9 shows the nucleotide sequence of 9D33 Heavy chain with primer, CDR and constant region sites marked. (Seq. ID No. 33).

Fig. 10 shows the amino acid sequence of 9D33 Heavy chain with primer, CDR and constant region sites marked. (Seq. ID No. 23).

Fig.11 shows the nucleotide sequence of 9D33 light chain with primer, CDR and constant region sites marked. (Seq. ID No. 38).

Fig. 12 shows the amino acid sequence of 9D33 light chain with primer, CDR and constant region sites marked. (Seq. ID No. 28).

Detailed Description of the Invention

Page 23, please amend the page as follows:

The above sequences for hMab TSHRI can also be seen by reference to Figures 4,5, 6 and 7, wherein:

Figure 4 shows the hMab TSHRI heavy chain nucleotide sequence, along with the adjacent constant region, ~~with- Figure 4a giving the nucleotide sequence per se ; Figure 4b giving the nucleotide sequence~~ annotated with the PCR primer, CDRI, CDRII, CDRIII and constant regions ;

Figure 5 shows the hMab TSHR1 heavy chain amino acid sequence, along with the adjacent constant region, ~~with- Figure 5a giving the amino acid sequence per se ; Figure 5b giving the amino acid sequence~~ annotated with the CDRI, CDRII, CDRIII and constant regions;

Figure 6 shows the hMab TSHRI light chain nucleotide sequence~~, with- Figure 6a giving the nucleotide sequence per se ; Figure 6b giving the nucleotide sequence~~ annotated with the PCR primer, CDRI, CDRII and CDRIII regions ; and

Figure 7 shows the hMab TSHR1 light chain amino acid sequence~~, with- Figure 7a giving the amino acid sequence per se ; Figure 7b giving the amino acid sequence~~ annotated with the CDRI, CDRII and CDRIII regions.

Page 24, please amend the first paragraph as follows

It will be appreciated from the above that for the VH chain of hMab TSHR1 the nucleotide sequences of the CDRI, CDRII and CDRIII regions as shown in Figure ~~4b~~ 4 correspond to the VHCDRI., VHCDRII and VHCDRIII sequences shown in SEQ ID NO. s 11, 12 and 13 respectively, and that the amino acid sequences of the CDRI, CDRII and CDRIII regions as shown in Figure ~~5b~~ 5 correspond to the VIqCDRI, VHCDRII and VHCDRIII sequences shown in SEQ ID NO. s 2, 3 and 4 respectively.

Pages 24, last partial paragraph, Page 25 and page 26, first partial paragraph are amended as follows:

The above sequences for 9D33 can also be seen by reference to Figures 9, 10, 11 and 12, wherein:

Figure 9 shows the 9D33 heavy chain nucleotide sequence, along with the adjacent constant region, ~~with- Figure 9a giving the nucleotide sequence per se; Figure 9b giving the nucleotide sequence~~ annotated with the PCR primer, CDRI, CDRII, CDRIII and constant regions;

Figure 10 shows the 9D33 heavy chain amino acid sequence, along with the adjacent constant region~~, with- Figure 10a giving the amino acid sequence per se ; Figure 10b giving the amino acid sequence~~ annotated with the PCR primer, CDRI, CDRII, CDRIII and constant regions;

Figure 11 shows the 9D33 light chain nucleotide sequence~~, with- Figure 11a giving the nucleotide sequence per-se ; Figure 11b giving the nucleotide sequence~~ annotated with the PCR primer, CDRI, CDRII, CDRIII and constant regions;

Figure 12 shows the 9D33 light chain amino acid sequence, ~~with- Figure 12a giving the amino acid sequence per se ; Figure 12b giving the amino acid sequence~~ annotated with the PCR primer, CDRI, CDRII, CDRIII and constant regions.

It will be appreciated from the above that for the V, chain of 9D33 the nucleotide sequences of the CDRI, CDRII and CDRIII regions as shown in Figure ~~9b~~ 9correspond to the VHCDRI, VHCDRII and VHCDRIII sequences shown in SEQ ID NO. s 30,31 and 32 respectively, and that the amino acid sequences of the CDRI, CDRII and CDRIII regions as shown in Figure ~~10b~~ 10 correspond to the VHCDRI, VHCDRII and VHCDRIII sequences shown in SEQ ID NO. s 20, 21 and 22 respectively. It will also be appreciated from the above that for the VL chain of 9D33 the nucleotide sequences of the CDRI, CDRII and CDRIII regions as shown in Figure ~~11b~~ 11 correspond to the VLCDRI, VLCDRII and VLCDRIII sequences shown in SEQ ID NO. s 35,36 and 37 respectively, and that the amino acid sequences of the CDRI, CDRII and CDRIII regions as shown in Figure ~~12b~~ 12 correspond to the VLCDRI, VLCDRII and VLCDRIII sequences shown in SEQ ID NO. s 25,26 and 27 respectively.

Page 33, please amend the first paragraph as follows:

A method according to the present invention for the detection of autoantibodies as described above is particularly advantageous in terms of the level of sensitivity that can be achieved by use thereof. This can be further illustrated by reference to the Examples and Figures, where Figure ~~3a~~ 3B shows a graphical representation of a comparison between an assay for TSHR autoantibodies based on hMAb TSHR1- biotin and earlier assays. The sensitivity of the assay based on hMAb TSHRI-biotin is clearly superior according to concentration of the international standard NIBSC 90/672 detectable. This was confirmed in a study of sera from 72 patients with Graves'disease shown in Figure ~~3b~~ 3C.

Page 67, please amend the paragraph starting on line 3 as follows:

The ability of different concentrations of hMAb TSHR1 IgG and Fab to inhibit labelled TSH binding to the TSH receptor is shown in Figure 1. As can be seen in Figure 1 as little as 1 ng/mL of these preparations inhibited TSH binding with more than 90% inhibition being obtained with 1000ng/mL. TSMAb TSHR1 IgG and Fab also stimulated cyclic AMP production in CHO cells transfected with the TSH receptor as shown in Figure 2. As little as l ng/mL of hMAb TSHRI IgG or Fab caused strong stimulation of cyclic AMP. Similar levels of stimulation were observed with 0.l ng/mL porcine TSH and l0 ng/mL of human TSH. Comparison of the ability of the serum from the original lymphocyte donor (taken at the same time as the blood sample for lymphocyte isolation) to inhibit labelled TSH binding to the TSH receptor and to stimulate cyclic AMP production in TSH receptor transfected CHO cells is shown in Figure 3A. Inhibition of TSH binding could be detected with serum diluted 500x whereas stimulation of cyclic AMP could be detected with serum diluted 5000x.

Pages 67-68, please amend the paragraph spanning the pages as follows:

As shown in Table 4 hMAb TSHRI-biotin bound to TSH receptor coated ELISA plates and the binding was inhibited by the international reference preparation NIBSC 90/672 and serum from patients with Graves'disease. Inhibition of binding was not observed by sera from healthy blood donors. Figure ~~3a~~ 3B shows a graphical representation of a comparison between an assay for TSHR autoantibodies based on hMAb TSHR1-biotin and earlier assays. The sensitivity of the assay based

on hMAb TSHR1-biotin is clearly superior according to concentration of the international standard NIBSC 90/672 detectable. This was confirmed in a study of sera from 72 patients with Graves'disease shown in Figure ~~3b~~ 3C. Healthy blood donor sera (n = 100) and sera from subjects with non-thyroid diseases (n = 43) gave respectively values of up to 10% inhibition of hMAb TSHR1 binding and up to 11% inhibition of TSH binding in this study. hMAb TSHR1 IgG did not react with full length TSH receptor preparations on Western blot analysis nor did it react well with 35S-labelled full length TSH receptor in the immunoprecipitation assay nor in the TSH receptor peptide ELISA. This lack of reactivity indicates that hMAb TSHR1 reacts with conformational rather than linear epitopes on the TSH receptor.